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(71) Applicant (for all designated States except US):
PHARMA BIOTECH LIMITED [CY/CY]; Agias
Varvaras 24, Archangelos, Nicosia (CY).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ANZAGHI**,
Piergiorgio [IT/IT]; Via Steffenini, 22, I-20078 San
Colombano al Lambro (IT). **STEFLL**, Rosanna [IT/IT];
Via Foppa, 8, I-27100 Pavia (IT).

(74) Agent: **GERVASI, Gemma**; Notarbartolo & Gervasi
S.P.A., Corso de Porta Vittoria, 9, I-20122 Milano (IT).

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(54) Title: ANTIBIOTICS ADDUCTS WITH NATURAL POLYSACCHARIDE POLYMERS IN THE FORM OF AQUEOUS SOLUTIONS.

(57) Abstract: Antibiotics adducts with natural polysaccharide polymers in the form of aqueous solutions, endowed with better antibacterial activity if compared to the starting antibiotic.

ANTIBIOTIC ADDUCTS WITH NATURAL POLYSACCHARIDE POLYMERS IN THE FORM OF AQUEOUS SOLUTIONS

FIELD OF THE INVENTION

The present invention concerns natural polysaccharide polymer-antibiotic adducts
5 in the form of aqueous solutions, having improved antibacterial activity if compared to that of the corresponding antibiotic.

STATE OF THE ART

Most of difficulties that arise during chemotherapeutic treatment reside in that certain active ingredient do not possess optimum pharmacokinetic characteristics.
10 One of the approaches used by the pharmaceutical technique to overcome the drawbacks, due to poor bioavailability or limited action duration following oral or parenteral administration, consists in binding the antibiotic to natural or synthetic inert and biocompatible polymers. However, the experiments in the field of conjugation with polymers have had limited success and above all they are poorly
15 predictable. Grishin G.I., Tr. Leningrad. Khim.- Farm. Inst. (1969), 27, 113-18 describes the interaction between penicillins or tetracyclines and some natural polysaccharides. The result of these interactions is far from being both quantifiable as well as qualifiable: in fact, in some cases no or poor interaction is observed, in other cases the interaction is established but without any effect on the activity of
20 the antibiotic. This may be due to many causes such as the nature of the bond and the relationship between the molecules.

Antibiotic-polymer associations which have proved advantageous concern well defined classes of antibiotics or individual antibiotics, and are often characterized by the formation of covalent or ionic bond complexes or conjugates.

25 The patent application EP 0 392 487 (in the name of Takeda Chemical Industries Ltd.) describes a complex between an anthracyclenic antibiotic carrying an amino sugar residue and a polyanion described as a natural or synthetic polymer carrying negatively charged residues, so as to form ionic bonds with the residues of the positively charged amino sugar. As regards the antibiotic itself, this complex has
30 improved stability characteristics at neutral pH, this allows the production of slow release preparations without irritative effects on tissues.

The patent EP 0 428 486 (in the name of Sandoz Ltd.) claims a hydrosoluble

conjugate of polymyxin and a vehicle, for instance a polysaccharide like dextran, with longer half-life and higher strength of the native polymyxin. The bond that characterizes this conjugate is of aminic or carbamate type, i.e. it is a covalent bond.

5 Molteni L., Optimization of Drug Delivery, Alfred Benzon Symposium 17, publishers: Hera Bundgaard, Anne Bagger Hansen, Helmer Hafod, Munksgaard, Copenhagen, 1982, deals with the interaction of various types of substances, and among them of certain antibiotics, and polysaccharides, for example dextrans or inulin. The type of interaction is clearly covalent since it is emphasized that, given
10 the poor chemical reactivity of the polysaccharides and because of the presence of numerous hydroxylic groups in these substances, the interaction is based on ester type bonds with substances having carboxylic groups, or the hydroxylic groups can be oxidized to aldehydes or be replaced with reactive groups. Besides not providing positive results, the antibiotic-polymer conjugate of covalent
15 or ionic bond represents an expensive and complex approach as far as regulatory affairs are concerned to the solution of the aforesaid pharmacokinetic problems since, dealing with chemical entities based on strong bonds, namely covalent and ionic, these conjugates, being pro-drugs, are considered as new compounds and they must be chemically characterised, their pharmacodynamic profile and clinical
20 efficacy must also be studied.

The patent application EP 0 438 747 (in the name of Shionogi Seiyaku Kabushiki Kaisha) claims a stable freeze-dried substance composed of a glycopeptide antibiotic and a hydrosoluble saccharide such as a polysaccharide like dextran, that is used in low percentages and has a stabilizing function during freeze-drying.

25 The glycopeptide antibiotics, such as vancomycin, are drugs of an extremely particular profile, they are chemically very complex, at times unable to be administered orally and, as in the case of vancomycin, nor even intramuscularly, and besides they are highly nephrotoxic.

SUMMARY

30 It has now been surprisingly found that solutions of antibiotics associated with natural polysaccharides have a microbiological activity and therapeutic efficacy which are equal to or higher than the same free antibiotic, although they contain it

in reduced doses and therefore they show lower toxicity.

The present invention relates to an adduct of an antibiotic with a natural polysaccharide polymer in the form of an aqueous solution, characterized in that the percentage of said active ingredient is comprised between 40 and 80% in weight based on the total weight of the adduct.

This adduct is prepared with a simple process of technical realization with low costs.

The present invention further relates process for preparing this aqueous solution comprising the dissolution of the two components of the adduct in distilled water, so as to obtain a clear solution.

The present invention also concerns pharmaceutical compositions including as the active ingredient antibiotics adducts of antibiotics with natural polysaccharide polymers in the form of aqueous solutions, in association with suitable excipients or diluents.

DETAILED DESCRIPTION OF THE INVENTION

The natural polysaccharide-antibiotic adducts in the form of aqueous solution according to the present invention, in which the interaction between the two components is based on non-covalent and non-ionic bonds, are preferably contained in the aqueous solution in a concentration of between 0.5 and 60% in weight based on the total weight of the aqueous solution.

More specifically, among the preferred antibiotics according to the present invention we mention cephalosporins namely ceftriaxone; aminoglycosides namely gentamycin and their aminocyclitol correlates namely spectinomycin.

The polysaccharides useful for the present invention are biocompatible and inert, and therefore they are free from pharmacological and toxicological type drawbacks. They are preferably selected from dextrans and inulin. Dextrans are particularly preferred for the purpose of the present invention.

Dextrans are hydrophilic and hydrosoluble polymers, stable to enzymatic attack, formed by linear chains of α -D-glucose molecules. They have molecular weights varying between 1,000 Dalton (dextran 1) and 110,000 Dalton (dextran 110). The dextrans with a molecular weight of lower than 4000 Dalton are completely excreted in the urine within 48 hours, while those with higher molecular weights

remain in circulation for longer periods of time. Preferred for the uses in the present invention are the dextrans of from 4 to 70, namely those having a molecular weight ranging from 4,000 to 70,000 Dalton.

The bond joining antibiotic and polysaccharide in the adduct of the present invention is of non-covalent and non-ionic type, and this is easily deduced from the preparation method of these adducts that envisages a simple co-solution of the polysaccharide and the antibiotic in water: this makes the hydrophilic interaction possible between the hydroxylic groups of the antibiotic and those of the polysaccharide through weak bonds, so called because they require less energy, to be broken, if compared to covalent or ionic bonds. As illustrated in Remington's Pharmaceutical Science, 18th ed., p. 186 seq., that calls these adducts "molecular complexes", the type of interaction involved can be of various types (from hydrogen, bond to hydrophobic interaction, to charge transfer).

The adducts of the present invention are obtained with simple, quick and economic processes if compared to the traditional approaches that envisage a covalent bond between the antibiotic and polysaccharide vehicle.

Optionally the process according to the present invention can envisage the presence, at the dissolution stage, of solubilizing and/or adjustment agents of the pH, and preservatives.

The antibiotic can be solubilized together with the natural polysaccharide to give a solution ready for oral or injectable use, or can be dissolved with a solvent solution in which the polysaccharide is present for an extemporaneous preparation at the moment of use. In this latter case the antibiotic in solid form is used as such in the form of a powder, a lyophilized or spray dried substance.

In the case of the preparations intended for injectable use, the distilled water to be used in the process of the present invention is depyrogenated and sterile distilled water for injectable use; in addition the solution of the antibiotic and of the polysaccharide or of the polysaccharide alone, is sterilized through 0.2 μ m porosity filters, then placed in phialoids, previously depyrogenated and sterilized, operating in a sterile environment under a hood with a laminar flow. The active ingredient in solid form for extemporaneous use must be apyrogenous and placed into depyrogenated and sterilized small bottles under a hood with laminar flow.

In the case of preparations for oral use, distilled water is used and the solution is filtered on filters of 0.45 µm porosity.

The formation of these adducts favourably alters certain pharmacokinetic characteristics of the antibiotic. In fact, if orally administered, these compositions
5 can increase the solubility of the antibiotic and consequently its bioavailability. In the case of injective therapy, the presence of the polysaccharide allows the time duration the drug remains in circulation and therefore the action duration.

The activity of the adducts of ceftriaxone and spectinomycin was assessed *in vivo*, whereas that of the adducts of gentamycin was assessed both *in vitro* and *in vivo*.

10 Likewise the present invention relates to the use of natural polysaccharide-antibiotic adducts based on non-covalent and non-ionic bonds for the treatment of pathologies in humans and animals.

The following examples of the present invention are reported for illustrative but not limitative purposes.

15 **EXAMPLE 1- Extemporaneous solution of the adduct: 60% ceftriaxone - 40% dextran 5**

4 g of dextran 5 are dissolved in 20 ml of apyrogenous w.f.p. distilled water. The solution is filtered on a 0.2µm porosity filter in a sterile environment and placed in sterilized and apyrogenous vials in a ratio of 2 ml each.

20 Under a hood with laminar flow in a sterile environment, 6 g of ceftriaxone corresponding to 7.15 g of disodic hemiheptahydrate salt are divided into 10 sterilized and apyrogenous small bottles for obtaining a filling of base ceftriaxone in each bottle.

The 600 mg of ceftriaxone are dissolved with 2 ml of solvent containing 400 mg of
25 dextran 5.

The ceftriaxone titre, calculated by HPLC method (FUI X ed., p. 811), is 60.1%.

1 g of adduct containing 60% of active ingredient is constituted in solution.

EXAMPLE 2- Solution of the adduct 42% gentamycin - 58% dextran 4

0.72 grams of sodium methylparahydroxybenzoate are dissolved in 200 ml of
30 boiling depyrogenated distilled water, which 80 mg of sodium propylparahydroxybenzoate and 40 mg of EDTA are added to, while bringing the solution to 300 ml. 128 mg of Na₂S₂O₅ and 1.68 g of base gentamycin (titre 100%)

are then added. 2.32 g. of dextran 4 and further distilled water are then poured under stirring up to reaching a total volume of 400 ml.

The adduct solution was filtered with a sterile filter of 0.2 μ m porosity and placed into depyrogenated and sterilized phialoids in a ratio of 50 ml each under hood with a laminar flow.

The pH value is 4.6 and the gentamycin titre, calculated by means of microbiological dosage, is 42% (titration by diffusion method, FUI X ed. p. 135).

EXAMPLE 3 – Extemporaneous solution of the adduct 50% gentamycin - 50% inulin

Under a laminar flow hood, 16.6 g of gentamycin sulphate corresponding to 10 g base (titre 100%) are placed in 20 sterilized and depyrogenated small bottles for obtaining a filling of 0.5 g by weight in each bottle. The small bottles are lastly corked and ring sealed. Still operating under the hood, a solution is prepared, consisting of 10 g of inulin in 100 ml of w.f.p. apyrogenous distilled water that is filtered and put into 20 vials of 5 ml each. By solubilizing the gentamycin contained in one small bottle with the solvent of one vial, a solution is constituted at pH= 4.28 with a gentamycin titre of 49.92% (determination by means of microbiological test as in Ex. 1). One gram of adduct therefore corresponds to 0.5 g of base gentamycin.

EXAMPLE 4 – Solution of the adduct 60% spectinomycin - 40% dextran 5

40 grams of dextran 5 are dissolved in 600 ml of distilled water and 89.4 g of spectinomycin hydrochloride equal to 60 g base are added to the solution under magnetic stirring. The final volume is adjusted to 1 l with distilled water and the solution is filtered through a filter of 0.45 μ m porosity in a bottle of 1 l capacity.

The spectinomycin titre is 59.8% (method HPLC FUI X ed. page 1977).

EXAMPLE 5- In vivo activity of the Ceftriaxone adducts

The effectiveness of the 60% ceftriaxone adduct of example 1 was compared with that of the respective full dose active ingredient. The ceftriaxone and the adduct, at a suitable dilution in w.f.p. water, were administered by intraperitoneal route to common albino mice of 28 g average weight, previously infected with a strain of *Staphylococcus aureus* (that does not show resistance to the antibiotic considered) and which therefore had developed ulcerative dermatitis with localized

abscesses and popodermatitis (mastitis). The treatment was continued for 5 days with injections every 24 hours. After this period a bacteriological test was performed by inoculating, on plate, the material taken from the skin of the mice by means of swabs. The results are contained in Table I.

5

Table I

Compound	N.° infected subjects	Post-infection clinical manifestations	Bacteriological examination after 5 days of therapy		Recovery %
			positive	negative	
CEFTRIA	8	YES	1	7	87.5
XONE	2	NO	0	0	
Adduct of	9	YES	0	9	100
example 1	1	NO	0	0	
Infected control	10	YES	10	0	
Non-infected control	10	NO			

EXAMPLE 6 - *in vitro* activity of the gentamycin adducts

The inhibition halos of a gentamycin solution and of solutions of the adduct 2 and 3 were obtained with the diffusion method (Official Italian Pharmacopeia, X ed., p. 135) by using a Mueller-Hinton Medium Difco culture medium (with low thymine and thymidine content) in 9 cm diameter sterile Petri plates and Tryptic Soy Broth (Difco).

For the sensitivity test small paper discs were prepared soaked both with the antibiotic at particular concentrations, and the discs and with the adduct at equal doses, but at lower concentration of the active ingredient.

To produce the bacterial growth: a strain of *Staphylococcus aureus* ATCC 6538 P

(strain A) and a field strain of *Staphylococcus aureus* (strain B) were used.

Broth cultures were prepared by putting a bacterial patina loop of a 12 h culture in agar in a test tube containing 5 ml of Sterile Tryptic Soy Broth and then incubated at 37° C for 4 h.

- 5 If necessary, the suspensions were diluted with sterile water to obtain a turbidity similar to the reference standard (0.5 McFarland). 150 ml of Mueller-Hinton Medium were sterilized in autoclave at 121°C for 15 minutes, a part was put in 9 cm diameter sterile Petri plates and left to solidify, the remaining was cooled to \approx 45°C and inoculated with 1.5 ml of the bacterial suspensions previously prepared
- 10 and poured on the surface of the solidified agar in a ratio of 10 ml per plate. The sown plates were kept to open dry under a laminar flow hood for 15 minutes and then the discs were placed on the surface. 4 discs were placed in each plate: the adduct and the antibiotic the two desired concentrations. The plates thus prepared, 5 for each test, were incubated upside down at 37°C for 16 h and after
- 15 this time the inhibition halos were determined.

The results obtained are contained in Table II

Table II

Antibiotic	Dose (μ g)	Antibiotic inhibition halos (mm) on strain		Adduct	Dose (μ g)	Adduct inhibition halos (mm) on strain	
		A	B			A	B
Gentamycin	4	13.1	12.2	Example 2	4	12.6	12.8
	6	15.4	12.9		6	14.0	13.4
				Example 3	4	12.9	12.0
					6	14.3	13.0

20 **EXAMPLE 7 *in vivo* activity of the 42% gentamycin adduct**

Solutions of gentamycin and solutions of the adduct of example 2 were "double blind" experimented on piglets weighing 5-8 Kg and suffering from Colibacillosis with manifestation of neonatal diarrhoea.

72 animals in total were considered, divided into 2 groups A and B each containing

36 animals, treated with intramuscular administration of 1 ml respectively of solution A and B every 12 hours for 5 days.

Solution A contained 10 mg of base gentamycin, while solution B contained 10 mg of the adduct of example 2, equal to 4.2 mg of base gentamycin.

- 5 The results of the study are shown in Table III.

Table III

Experimentation group	N° of piglets treated	Compound	N° of piglets cured	Recovery %
A	36	Gentamycin	20	55.5
B	36	Adduct of example 1	36	100

EXAMPLE 8- *in vivo* activity of the spectinomycin adduct

- 10 A solution of spectinomycin and of the respective adduct of example 4 were administered to chickens suffering from chronic respiratory disease.

A total of 100 chickens of 1 Kg average weight were treated for 7 days with 500 ml of solution (equal to 50 g of active product) diluted in 100 l of drinking water. More precisely 50 animals, identified as group 1, were watered with 100 l of water
 15 containing the solution of 50 g of spectinomycin and the other 50, belonging to group 2, with 100 l in which was diluted the adduct solution containing 30 g of spectinomycin.

The results of the study are shown in Table IV.

Table IV

Experimentation group	N° of chickens treated	Compound	N° of chickens cured	Recovery %
1	50	Spectinomycin	45	90
2	50	Adduct of example 4	43	86

The adducts of the present invention have shown, in the *in vitro* and *in vivo* tests of antimicrobial activity, a comparable activity or slightly higher than that of the active principle alone, although they contain it in lower amounts, thus reducing the cost of the therapy.

- 5 This translates into a reduction of the adduct toxicity with equal efficacy.

These adducts, obtained with a quick, economic process, are suitable for the treatment of infections due to Gram-positive and Gram-negative bacteria in animals and humans.

CLAIMS

1. Adduct of an antibiotic with a natural polysaccharide polymer in the form of aqueous solution, wherein the percentage of said antibiotic is comprised between 40 and 80% by weight based on the total weight of the adduct.
- 5 2. Adduct according to claim 1, wherein said adduct is contained in the aqueous solution at concentrations comprised between 0.5 and 60% by weight.
3. Adduct according to anyone of claims 1-2, wherein the antibiotic is selected from the group consisting of: cephalosporins, aminoglycosides, aminocyclitolics:
4. Adduct according to any one of the claims 1-3, wherein the natural type
10 polysaccharide polymer is selected from the group consisting of: dextrans and inulin.
5. Adduct according to claim 4, wherein in the natural polysaccharide polymer is dextran.
6. Adduct according to claim 4, wherein dextrans 4-70 are used.
- 15 7. A process for preparing the adducts according to any one of the claims 1-6, comprising the dissolution of the two components of the adduct in distilled water, so as to obtain a clear solution.
8. The process for preparing the adducts according to claim 7, in the form of an extemporaneous aqueous solution for oral or injectable use, comprising the
20 solubilization of the antibiotic together with the natural polysaccharide.
9. The process according to claim 7 for preparing an extemporaneous aqueous solution for oral or injectable use, comprising the dissolution of the antibiotic with a solvent in which the polysaccharide is present.
10. The process according to claim 9 wherein the antibiotic is used in solid form as
25 powder as such, as lyophilized or spraydried substance.
11. The process according to any one of claims 7-10, wherein for preparing the injectable solutions, the solution of antibiotic and of polysaccharide or only of the polysaccharide is sterilized through filters of 0.2 μm porosity, then placed into phialoids previously depyrogenated and sterilized.
- 30 12. The process according to any one of claims 7-10, wherein distilled water is used for preparing the solutions for oral use and the solution is filtered through filters of 0.45 μm porosity.

13. A pharmaceutical composition comprising as the active ingredient at least one adduct of antibiotic with a natural polysaccharide polymer in the form of an aqueous solution according to any one of the claims 1-6, in association with suitable excipients or diluents.

5 14. The composition according to claim 13, for oral use.

15. The composition according to claim 13 for injectable use.

INTERNATIONAL SEARCH REPORT

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PC 1, 10 01/02172

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61P31/00

According to International Patent Classification (IPC) or to both national classification and IPC

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 00 78287 A (ANZAGHI PIERGIORGIO ; STEFLI ROSANNA (IT); ISTITUTO BIOCHIMICO PAVE) 28 December 2000 (2000-12-28) the whole document	1-15
X	US 4 315 002 A (MAURER ROBERT) 9 February 1982 (1982-02-09) the whole document	1-15
X	US 4 663 316 A (LIAO WEICHI ET AL) 5 May 1987 (1987-05-05) examples 1,2,11	1,7-15
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3018

Authorized officer

Pacreu Largo, M

INTERNATIONAL SEARCH REPORT

Inten Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MITSURU TASHIRO ET AL: "INCLUSION COMPLEX OF A NEW ORALLY ACTIVE CEPHALOSPORIN ME1207 WITH SS-CYCLODEXTRIN" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 40, no. 6, 1 June 1992 (1992-06-01), pages 1623-1625, XP000292450 ISSN: 0009-2363 the whole document	1,3,7-15
X,P	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 20, 10 July 2001 (2001-07-10) & JP 2001 058994 A (EISAI CO LTD), 6 March 2001 (2001-03-06) abstract	1,7-15

INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/JP 01/02172

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0078287	A	28-12-2000	IT MI991085 A1 AU 5524200 A WO 0078287 A1 EP 1180019 A1	20-11-2000 09-01-2001 28-12-2000 20-02-2002
US 4315002	A	09-02-1982	DE 2925009 A1 AT 3814 T DE 3063858 D1 EP 0021009 A2 JP 56007724 A	08-01-1981 15-07-1983 28-07-1983 07-01-1981 27-01-1981
US 4663316	A	05-05-1987	AU 581061 B2 AU 5441386 A CA 1237125 A1 DE 3669517 D1 DK 100886 A EP 0206490 A2 JP 62004293 A ZA 8602575 A	09-02-1989 08-01-1987 24-05-1988 19-04-1990 29-12-1986 30-12-1986 10-01-1987 26-11-1986
JP 2001058994	A	06-03-2001	NONE	